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=> d his

     (FILE 'HOME' ENTERED AT 12:28:02 ON 17 JAN 2006)

     FILE 'MEDLINE, CAPLUS, BIOSIS' ENTERED AT 12:28:32 ON 17 JAN 2006
L1         33098 S LEPTIN
L2         83497 S ANGIOGENESIS
L3           570 S ANG2
L4           270 S L1 (L) L2
L5           183 S L2 (L) L3
L6            86 DUP REM L5 (97 DUPLICATES REMOVED)
L7            37 S L6 AND PY<2003
L8        496701 S ENDOTHEL?
L9            33 S L7 (L) L8
L10           10 S L9 AND INHIBITOR
                 E RUBINSTEIN MENCACHEM /AU
L11          246 S E1
                 E COHEN BATYA /AU
L12           41 S E3 OR E2
                 E BARKAN DALIT /AU
L13           15 S E3
L14          271 S L11 OR L12 OR L13
L15            1 S L14 AND LEPTIN AND ANGIOGENESIS
```

L15 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN

TI **Leptin** for use in inhibition of endothelial cell proliferation optionally together with VEGF inhibitors

IN **Rubinstein, Menachem; Cohen, Batya; Barkan, Dalit**

AB Disclosed is the use of **leptin**, optionally together with VEGF inhibitors, in inhibition of endothelial cell proliferation and modulation of **angiogenesis**, for use in the female reproductive tract or for use in adipose tissue regression. Pharmaceutical compns. are also claimed.

ST **leptin** VEGF antagonist compn endothelium proliferation **angiogenesis** inhibition

IT Blood vessel
(endothelium; **leptin** for use in inhibition of endothelial cell proliferation optionally together with VEGF inhibitors)

IT Reproductive tract
(female; **leptin** for use in inhibition of endothelial cell proliferation in female reproductive tract optionally together with VEGF inhibitors)

IT Vascular endothelial growth factor receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene flt 1; pharmaceutical compns. for inhibiting endothelial cell proliferation comprising **leptin** or **leptin** analog or derivative optionally with inhibitor of VEGF action or synthesis and/or inhibitor of **angiogenesis**)

IT **Angiogenesis** inhibitors
(**leptin** for use in inhibition of endothelial cell proliferation and for modulation of **angiogenesis** optionally together with VEGF inhibitors)

IT Antiobesity agents
(**leptin** for use in inhibition of endothelial cell proliferation and for regression of adipose tissue optionally together with VEGF inhibitors)

IT Proliferation inhibition
(**leptin** for use in inhibition of endothelial cell proliferation optionally together with VEGF inhibitors)

IT Drug delivery systems
(pharmaceutical compns. for inhibiting endothelial cell proliferation comprising **leptin** or **leptin** analog or derivative optionally with inhibitor of VEGF action or synthesis and/or inhibitor of **angiogenesis**)

IT 194368-66-6, Angiopoietin 2
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(**leptin** for use in inducement of angiopoietin 2 optionally together with VEGF inhibitors)

IT 83-67-0, Theobromine 145-63-1, Suramin 519-37-9, 7-(β-Hydroxyethyl)theophylline 961-45-5, 8-Phenyltheophylline 14114-46-6, DMPX 37270-94-3, Platelet factor-4 53902-12-8, Tranilast 147700-11-6, 8-(3-Chlorostyryl)caffeine 169494-85-3, **Leptin** 169494-85-3D, **Leptin**, homologs and derivs. 200725-10-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**leptin** for use in inhibition of endothelial cell proliferation optionally together with VEGF inhibitors)

IT 127464-60-2, Vascular endothelial growth factor
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(**leptin** for use in inhibition of endothelial cell proliferation optionally together with VEGF inhibitors)

=> d l15 ti au so py

L15 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN

TI **Leptin** for use in inhibition of endothelial cell proliferation optionally together with VEGF inhibitors

IN **Rubinstein, Menachem; Cohen, Batya; Barkan, Dalit**

SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2

PY 2001
2001
2001
2001
2005
2002
2002
2003
2003
2003
2002
2005

=> d l10 1-10 ti au py so kwic

L10 ANSWER 1 OF 10 MEDLINE on STN
TI A computer algorithm describing the process of vessel formation and maturation, and its use for predicting the effects of anti-angiogenic and anti-maturation therapy on vascular tumor growth.
AU Arakelyan L; Vainstein V; Agur Z
PY **2002**
SO Angiogenesis, **(2002)** 5 (3) 203-14.
Journal code: 9814575. ISSN: 0969-6970.
SO Angiogenesis, **(2002)** 5 (3) 203-14.
Journal code: 9814575. ISSN: 0969-6970.
AB . . . forward an algorithm describing the three principal interconnected sub-processes that influence tumor and vasculature dynamics: (i) tumor cell proliferation (ii) **angiogenesis**, that is, the formation and regression of immature vessels (IV), and (iii) maturation, i.e., the formation and destabilization of mature. . . and organ levels. Implementing this complex algorithm in a computer model, one can evaluate the correlations between various factors influencing **angiogenesis** and their influence on tumor progression at any given moment. Moreover, the computer simulations enable analysis of the versatile effects. . . blood vessels, as well as on the induction of an array of relevant growth factors such as angiopoietin-1 (Ang1), angiopoietin-2 (**Ang2**), vascular **endothelial** growth factor (VEGF) and platelet-derived growth factor (PDGF). Simulation results suggest that vessel maturation and destabilization of MV drive the. . .
CT *Algorithms
***Angiogenesis Inhibitors: TU, therapeutic use**
Disease Progression
Endothelial Growth Factors: GE, genetics
Humans
Intercellular Signaling Peptides and Proteins: GE, genetics
Lymphokines: GE, genetics
Models, Biological
*Neoplasms: BS, blood supply
Neoplasms: DT, drug therapy
*Neoplasms: PA, pathology
*Neovascularization, Pathologic
Research Support, Non-U.S. Gov't
Vascular Endothelial Growth Factor A
Vascular Endothelial Growth Factors
CN 0 (Angiogenesis **Inhibitors**); 0 (**Endothelial** Growth Factors); 0 (Intercellular Signaling Peptides and Proteins); 0 (Lymphokines); 0 (Vascular **Endothelial** Growth Factor A); 0 (Vascular **Endothelial** Growth Factors)

L10 ANSWER 2 OF 10 MEDLINE on STN
TI Dual role of **Ang2** in postnatal **angiogenesis** and lymphangiogenesis.
AU Veikkola Tanja; Alitalo Kari
PY **2002**
SO Developmental cell, **(2002 Sep)** 3 (3) 302-4.
Journal code: 101120028. ISSN: 1534-5807.
TI Dual role of **Ang2** in postnatal **angiogenesis** and lymphangiogenesis.
SO Developmental cell, **(2002 Sep)** 3 (3) 302-4.
Journal code: 101120028. ISSN: 1534-5807.
AB . . . the opposing processes of vessel growth and regression. A new study in this issue of Developmental Cell shows that Angiopoietin-2 (**Ang2**), a ligand for the **endothelial** Tie2 receptor tyrosine kinase, has a dual function in the processes of postnatal **angiogenesis** and vascular remodeling. Also, **Ang2** signals are required for the proper development and function of the lymphatic vessels.
CT *Angiogenesis Inducing Agents: PH, physiology
Angiopoietin-2

Animals
*Blood Vessels: GD, growth & development
Blood Vessels: ME, metabolism
Embryo: ME, metabolism
Endothelial Growth Factors: GE, genetics
Endothelial Growth Factors: ME, metabolism
Endothelium, Vascular: CY, cytology
Endothelium, Vascular: ME, metabolism
*Lymphatic System: GD, growth & development
Lymphatic System: ME, metabolism
Mice
Mice, Knockout
Models, Biological
*Neovascularization, Physiologic
Platelet-Derived Growth Factor: ME, metabolism
Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors
Receptor Protein-Tyrosine Kinases: ME, metabolism
Signal Transduction
CN 0 (Angiogenesis Inducing Agents); 0 (Angiopoietin-2); 0 (**Endothelial** Growth Factors); 0 (Platelet-Derived Growth Factor); EC 2.7.1.112 (Receptor Protein-Tyrosine Kinases)

L10 ANSWER 3 OF 10 MEDLINE on STN
TI Angiopoietin-2 displays VEGF-dependent modulation of capillary structure and **endothelial** cell survival in vivo.
AU Lobov Ivan B; Brooks Peter C; Lang Richard A
PY **2002**
SO Proceedings of the National Academy of Sciences of the United States of America, **(2002 Aug 20)** 99 (17) 11205-10. Electronic Publication: 2002-08-05.
Journal code: 7505876. ISSN: 0027-8424.
TI Angiopoietin-2 displays VEGF-dependent modulation of capillary structure and **endothelial** cell survival in vivo.
SO Proceedings of the National Academy of Sciences of the United States of America, **(2002 Aug 20)** 99 (17) 11205-10. Electronic Publication: 2002-08-05.
Journal code: 7505876. ISSN: 0027-8424.
AB Modulation of Tie2 receptor activity by its angiopoietin ligands is crucial for **angiogenesis**, blood vessel maturation, and vascular **endothelium** integrity. It has been proposed that angiopoietins 1 (Ang1) and 2 (**Ang2**) are pro- and anti-angiogenic owing to their respective agonist and antagonist signaling action through the Tie2 receptor. The function of **Ang2** has remained controversial, however, with recent reports suggesting that in some circumstances, it may be pro-angiogenic. We have examined this. . . vivo model for studying the effects of vascular regulators. We show that in vivo, in the presence of endogenous vascular **endothelial** growth factor (VEGF)-A, **Ang2** promotes a rapid increase in capillary diameter, remodeling of the basal lamina, proliferation and migration of **endothelial** cells, and stimulates sprouting of new blood vessels. By contrast, **Ang2** promotes **endothelial** cell death and vessel regression if the activity of endogenous VEGF is inhibited. These observations support a model for regulation of vascularity where VEGF can convert the consequence of **Ang2** stimulation from anti- to pro-angiogenic.
CT . . . Apoptosis: DE, drug effects
*Capillaries: CY, cytology
Capillaries: DE, drug effects
Cell Division: DE, drug effects
*Cornea: BS, blood supply
***Endothelial Growth Factors: PD, pharmacology**
***Endothelium, Vascular: CY, cytology**
Endothelium, Vascular: DE, drug effects
Enzyme Inhibitors: PD, pharmacology
Humans
*Lymphokines: PD, pharmacology
*Muscle, Smooth, Vascular: CY, cytology
Muscle, Smooth, Vascular: DE, drug effects

Proteins:. . . pharmacology
*Proteins: PH, physiology
Rats
Rats, Sprague-Dawley
Recombinant Proteins: PD, pharmacology
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Vascular Endothelial Growth Factor A
Vascular Endothelial Growth Factors

CN 0 (Angiopoietin-2); 0 (**Endothelial** Growth Factors); 0 (Enzyme **Inhibitors**); 0 (Lymphokines); 0 (Proteins); 0 (Recombinant Proteins); 0 (Vascular **Endothelial** Growth Factor A); 0 (Vascular **Endothelial** Growth Factors)

L10 ANSWER 4 OF 10 MEDLINE on STN

TI Expression of angiopoietin-1, angiopoietin-2, and Tie2 genes in normal ovary with corpus luteum and in ovarian cancer.

AU Hata Kohkichi; Udagawa Jun; Fujiwaki Ritsuto; Nakayama Kentaro; Otani Hiroki; Miyazaki Kohji

PY **2002**

SO Oncology, **(2002)** 62 (4) 340-8.
Journal code: 0135054. ISSN: 0030-2414.

SO Oncology, **(2002)** 62 (4) 340-8.
Journal code: 0135054. ISSN: 0030-2414.

AB OBJECTIVE: The recent discovery of angiopoietin-1 (Ang1) and angiopoietin-2 (**Ang2**) has provided novel and important insights into the molecular mechanisms of blood vessel formation. Ang1 and **Ang2** bind with similar affinity to the **endothelial** cell tyrosine kinase receptor Tie2. Our purpose was to assess the potential role of the Ang/Tie2 system in physiological and pathological **angiogenesis** in the ovary. METHODS: Ang1, **Ang2**, and Tie2 gene expression in 14 normal ovaries with corpus luteum (CL) and in 19 cases of ovarian cancer were. . . was presented by the relative yield of each gene to the beta(2)-microglobulin gene, respectively. Furthermore, cellular distribution of Ang1 and **Ang2** mRNA was examined by in situ hybridization, and localization of Tie2 was studied by immunochemistry. RESULTS: The Ang1, **Ang2**, and Tie2 gene expression in normal ovary with CL ranged from 0.18 to 1.06 (median 0.54), 0.31-2.64 (median 1.01), and. . . normal ovary with CL was significantly higher than that in ovarian cancer ($p = 0.0004$). The gene expression levels of **Ang2** and Tie2 were statistically the same in both groups. There was a significant correlation between Ang1 gene expression and Tie2. . . normal ovary with CL ($r = 0.619$, $p = 0.018$). No such significant correlation was found in ovarian cancer. Moreover, **Ang2** gene expression showed no significant correlation with the Tie2 gene expression either in normal ovary with CL or in ovarian cancer. Transcripts for Ang1 were observed in CL cells and **endothelial** cells around CL, and in tumor cells and **endothelial** cells at the periphery of tumor invasion. **Ang2** transcripts were expressed in the same patterns. Tie2 expression was positive primarily in the **endothelial** cells around CL and in those at the periphery of tumor invasion. CONCLUSION: Our results indicate that there is a difference in the Ang/Tie2 gene expression between physiological and pathological **angiogenesis** in the ovary. This finding may aid in the development of new therapeutic interventions for ovarian cancer.

CT . . .
Neoplasms: GE, genetics
Ovarian Neoplasms: ME, metabolism
*Ovary: ME, metabolism
*Proteins: GE, genetics
Proteins: ME, metabolism
RNA, Messenger: ME, metabolism
Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors
*Receptor Protein-Tyrosine Kinases: GE, genetics
Receptor Protein-Tyrosine Kinases: ME, metabolism
Receptor, TIE-2
Reverse. . .

L10 ANSWER 5 OF 10 MEDLINE on STN
TI Expression of angiopoietin-1 in human glioblastomas regulates tumor-induced angiogenesis: in vivo and in vitro studies.
AU Audero E; Cascone I; Zanon I; Previtali S C; Piva R; Schiffer D; Bussolino F
PY **2001**
SO Arteriosclerosis, thrombosis, and vascular biology, **(2001 Apr)** 21 (4) 536-41.
Journal code: 9505803. ISSN: 1524-4636.
SO Arteriosclerosis, thrombosis, and vascular biology, **(2001 Apr)** 21 (4) 536-41.
Journal code: 9505803. ISSN: 1524-4636.
AB To define a role for the angiopoietin/Tie2 system in astrocytoma **angiogenesis**, we examined the expression of angiopoietin-1 (Ang1) and angiopoietin-2 (**Ang2**) in these tumors by immunohistochemistry and in situ hybridization. Furthermore, we studied in vitro the effects elicited by glioblastoma cell-secreted Ang1 or by recombinant Ang1 on functions of **endothelial** cells (ECs). Our observations of astrocytomas show that a stage-specific induction of angiopoietins occurs and is correlated with angiogenic phases. . . vessels, Ang1 mRNA increased progressively in high-grade glioblastomas, in which the number of vessels was higher than in low-grade tumors. **Ang2** was detected in tumor cells and in ECs in high-grade astrocytomas, whereas its expression was negligible in low-grade tumors. Coculture of glioblastoma cell lines producing Ang1 with **endothelium** demonstrated a key role of this ligand in the control of EC network organization. We found that recombinant Ang1 in. . . results suggest that Ang1 directly acts on ECs by modulating cell-cell and cell-matrix associations and promoting the differentiation phase of **angiogenesis**.
CT . . . Membrane Glycoproteins: ME, metabolism
Membrane Glycoproteins: PD, pharmacology
*Neovascularization, Pathologic: ME, metabolism
Protein Biosynthesis
Proteins: ME, metabolism
Proteins: PD, pharmacology
Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors
Research Support, Non-U.S. Gov't
Tumor Cells, Cultured

L10 ANSWER 6 OF 10 MEDLINE on STN
TI Biological action of angiopoietin-2 in a fibrin matrix model of angiogenesis is associated with activation of Tie2.
AU Teichert-Kuliszewska K; Maisonpierre P C; Jones N; Campbell A I; Master Z; Bendeck M P; Alitalo K; Dumont D J; Yancopoulos G D; Stewart D J
PY **2001**
SO Cardiovascular research, **(2001 Feb 16)** 49 (3) 659-70.
Journal code: 0077427. ISSN: 0008-6363.
SO Cardiovascular research, **(2001 Feb 16)** 49 (3) 659-70.
Journal code: 0077427. ISSN: 0008-6363.
AB The **endothelial** cell (EC) specific tyrosine kinase receptor, Tie2, interacts with at least two ligands, angiopoietin-1 (Ang1) and angiopoietin-2 (**Ang2**). Ang1 stimulates Tie2 receptor autophosphorylation, while **Ang2** has been reported to inhibit Ang1-induced Tie2 receptor autophosphorylation. We studied the effects of Ang1 and **Ang2** in an in vitro model of **angiogenesis**. Human ECs (HUVEC), cultured on 3-D fibrin matrices, were treated with conditioned media (CM) from stably transfected cells expressing human Ang1 or **Ang2**, or with purified recombinant proteins. EC tube formation was measured as a differentiation index (DI), calculated as the ratio of. . . and 19.13+/-7.86, respectively) vs. control (DI: 2.73+/-1.68 and 2.15+/-1.45, respectively, both P<0.001). Interestingly, CM from two independent cell lines overexpressing **Ang2** also produced a significant increase in EC differentiation (DI: 9.22+/-3.00 and 9.72+/-4.84, both P<0.005 vs. control) although the degree of **angiogenesis** was significantly less then that seen with Ang1. Addition of Ang1* (a genetically engineered variant of naturally occurring

Ang1) or **Ang2** also resulted in dose dependent increases in DI, which were blocked by an excess of soluble Tie2 receptor (20 microg/ml). Both Ang1* and **Ang2** induced modest increases in [3H]thymidine incorporation into HUVECs (20 and 26%, respectively), which were inhibited by excess soluble Tie2. Although **Ang2** was unable to induce significant Tie2 receptor phosphorylation during a 5-min exposure, a 24-h pretreatment with **Ang2**, followed by brief re-exposure, produced Tie2 phosphorylation in HUVEC comparable to that produced by Ang1*. These results demonstrate for the first time that **Ang2** may have a direct role in stimulating Tie2 receptor signaling and inducing in vitro **angiogenesis**. Our findings suggest that the physiological role of **Ang2** is more complex than previously recognized: acting alternately to promote or blunt Tie2 receptor signaling in **endothelial** cells, depending on local conditions.

CT Analysis of Variance
Angiopoietin-1
Angiopoietin-2
Animals
Aorta
Blotting, Western
Cell Differentiation
Cell Division
Cell Line
Cells, Cultured
Dose-Response Relationship, Drug
***Endothelium, Vascular: ME, metabolism**
***Enzyme Inhibitors: PD, pharmacology**
Gels
Gene Transfer Techniques
Humans
Membrane Glycoproteins: GE, genetics
Membrane Glycoproteins: PD, pharmacology
Models, Biological
*Muscle, Smooth, Vascular: BS, blood supply
*Neoplasm Proteins: ME, metabolism
*Neovascularization, Physiologic
Proteins: GE, genetics
*Proteins: PD, pharmacology
*Proto-Oncogene Proteins
Rats
***Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors**
Receptor, TIE-2
Research Support, Non-U.S. Gov't

CN 0 (Agpt protein, rat); 0 (Angiopoietin-1); 0 (Angiopoietin-2); 0 (Enzyme **Inhibitors**); 0 (Gels); 0 (MEN1 protein, human); 0 (Membrane Glycoproteins); 0 (Neoplasm Proteins); 0 (Proteins); 0 (Proto-Oncogene Proteins); 0 (angiopoietin 1,. . .

L10 ANSWER 7 OF 10 MEDLINE on STN

TI Angiotensin AT(1) and AT(2) receptors differentially regulate angiopoietin-2 and vascular **endothelial** growth factor expression and angiogenesis by modulating heparin binding-epidermal growth factor (EGF)-mediated EGF receptor transactivation.

AU Fujiyama S; Matsubara H; Nozawa Y; Maruyama K; Mori Y; Tsutsumi Y; Masaki H; Uchiyama Y; Koyama Y; Nose A; Iba O; Tateishi E; Ogata N; Jyo N; Higashiyama S; Iwasaka T

PY **2001**

SO Circulation research, **(2001 Jan 19)** 88 (1) 22-9.
Journal code: 0047103. ISSN: 1524-4571.

TI Angiotensin AT(1) and AT(2) receptors differentially regulate angiopoietin-2 and vascular **endothelial** growth factor expression and angiogenesis by modulating heparin binding-epidermal growth factor (EGF)-mediated EGF receptor transactivation.

SO Circulation research, **(2001 Jan 19)** 88 (1) 22-9.
Journal code: 0047103. ISSN: 1524-4571.

AB . . . growth factor (EGF)-like growth factor (HB-EGF) release followed by transactivation of EGF receptor (EGFR). Although Ang II and HB-EGF induce **angiogenesis**, their link to the angiopoietin (Ang)-Tie2

system remains undefined. We tested the effects of Ang II on Ang1, **Ang2**, or Tie2 expression in cardiac microvascular **endothelial** cells expressing the Ang II receptors AT(1) and AT(2). Ang II significantly induced **Ang2** mRNA accumulations without affecting Ang1 or Tie2 expression, which was inhibited by protein kinase C **inhibitors** and by intracellular Ca(2+) chelating agents. Ang II transactivated EGFR via AT(1), and inhibition of EGFR abolished the induction of **Ang2**. Ang II caused processing of pro-HB-EGF in a metalloproteinase-dependent manner to stimulate maturation and release of HB-EGF. Neutralizing anti-HB-EGF antibody blocked EGFR phosphorylation by Ang II. Ang II also upregulated vascular **endothelial** growth factor (VEGF) expression in an HB-EGF/EGFR-dependent manner. AT(2) inhibited AT(1)-mediated **Ang2** expression and phosphorylation of EGFR. In an in vivo corneal assay, AT(1) induced **angiogenesis** in an HB-EGF-dependent manner and enhanced the angiogenic activity of VEGF. Although neither **Ang2** nor Ang1 alone induced **angiogenesis**, soluble Tie2-Fc that binds to angiopoietins attenuated AT(1)-mediated **angiogenesis**. These findings suggested that (1) Ang II induces **Ang2** and VEGF expression without affecting Ang1 or Tie2 and (2) AT(1) stimulates processing of pro-HB-EGF by metalloproteinases, and the released HB-EGF transactivates EGFR to induce **angiogenesis** via the combined effect of **Ang2** and VEGF, whereas AT(2) attenuates them by blocking EGFR phosphorylation. Thus, Ang II is involved in the VEGF-Ang-Tie2 system via. . .

CT . . .

Angiopoietin-1
Angiopoietin-2
Angiotensin II: PD, pharmacology
Animals
Calcium: ME, metabolism
Cells, Cultured
Cornea: BS, blood supply
Cornea: DE, drug effects
***Endothelial Growth Factors: GE, genetics**
Endothelium, Vascular: CY, cytology
Endothelium, Vascular: DE, drug effects
Endothelium, Vascular: ME, metabolism
Enzyme Activation: DE, drug effects
*Epidermal Growth Factor: PH, physiology
Gene Expression Regulation: DE, drug effects
. . . genetics
Maleimides: PD, pharmacology
Membrane Glycoproteins: GE, genetics
Naphthalenes: PD, pharmacology
Neovascularization, Physiologic: DE, drug effects
*Neovascularization, Physiologic: PH, physiology
Protein Kinase C: AI, antagonists & inhibitors
Protein Kinase C: ME, metabolism
Protein-Tyrosine-Phosphatase: ME, metabolism
*Proteins: GE, genetics
Pyridines: PD,. . . genetics
RNA, Messenger: ME, metabolism
Rabbits
Rats
Receptor Protein-Tyrosine Kinases: GE, genetics
Receptor, Angiotensin, Type 1
Receptor, Angiotensin, Type 2
Receptor, Epidermal Growth Factor: AI, antagonists & inhibitors
*Receptor, Epidermal Growth Factor: GE, genetics
Receptor, Epidermal Growth Factor: ME, metabolism
Receptor, TIE-2
Receptors, Angiotensin: AI, antagonists & inhibitors
*Receptors, Angiotensin: PH, physiology
Receptors, Cell Surface
Receptors, TIE
Research Support, Non-U.S. Gov't
Tetrazoles: PD, pharmacology

Time Factors
Trans-Activation (Genetics)
Tyrphostins: PD, pharmacology
Vascular Endothelial Growth Factor A
Vascular Endothelial Growth Factors

CN 0 (Agpt protein, rat); 0 (Angiopoietin-1); 0 (Angiopoietin-2); 0 (**Endothelial** Growth Factors); 0 (Imidazoles); 0 (Indoles); 0 (Lymphokines); 0 (Maleimides); 0 (Membrane Glycoproteins); 0 (Naphthalenes); 0 (Proteins); 0 (Pyridines); 0. . . Type 1); 0 (Receptor, Angiotensin, Type 2); 0 (Receptors, Angiotensin); 0 (Receptors, Cell Surface); 0 (Tetrazoles); 0 (Tyrphostins); 0 (Vascular **Endothelial** Growth Factor A); 0 (Vascular **Endothelial** Growth Factors); EC 2.7.1.112 (Receptor Protein-Tyrosine Kinases); EC 2.7.1.112 (Receptor, Epidermal Growth Factor); EC 2.7.1.112 (Receptor, TIE-2); EC 2.7.1.112 (Receptors,. . .

L10 ANSWER 8 OF 10 MEDLINE on STN

TI Angiopoietin-2 at high concentration can enhance **endothelial** cell survival through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway.

AU Kim I; Kim J H; Moon S O; Kwak H J; Kim N G; Koh G Y

PY **2000**

SO Oncogene, **(2000 Sep 14)** 19 (39) 4549-52.
Journal code: 8711562. ISSN: 0950-9232.

TI Angiopoietin-2 at high concentration can enhance **endothelial** cell survival through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway.

SO Oncogene, **(2000 Sep 14)** 19 (39) 4549-52.
Journal code: 8711562. ISSN: 0950-9232.

AB The angiopoietin-Tie2 system in **endothelial** cells is an important regulator of vasculogenesis and vascular integrity. High levels of angiopoietin-2 (**Ang2**) mRNA are observed in vascular activation during tumorigenesis. Although **Ang2** is known to be a naturally occurring antagonist of angiopoietin-1 (Ang1) in vivo, the exact function of **Ang2** itself is not known. Here, we found that a high concentration of **Ang2** (800 ng/ml) acts as an apoptosis survival factor for **endothelial** cells during serum deprivation apoptosis. The survival effect of high concentration **Ang2** was blocked by pre-treatment with soluble Tie2 receptor and the PI 3'-kinase-specific **inhibitors**, wortmannin and LY294002. Accordingly, 800 ng/ml of **Ang2** induced phosphorylation of Tie2, the p85 subunit of phosphatidylinositol 3'-kinase (PI 3'-kinase), and serine-threonine kinase Akt at Ser473 in the human umbilical vein **endothelial** cells; lower concentrations of **Ang2** (50 - 400 ng/ml) did not produce notable effects. These findings indicate that at high concentrations, **Ang2**, like Ang1, can be an apoptosis survival factor for **endothelial** cells through the activation of the Tie2 receptor, PI 3'-kinase and Akt, and thus may be a positive regulator of tumor **angiogenesis**. Oncogene (2000) 19, 4549 - 4552.

CT **1-Phosphatidylinositol 3-Kinase: AI, antagonists & inhibitors**
1-Phosphatidylinositol 3-Kinase: DE, drug effects
*1-Phosphatidylinositol 3-Kinase: ME, metabolism
Androstadienes: PD, pharmacology
Angiopoietin-2
Apoptosis:. . . drug effects
Cell Line
Cell Survival: DE, drug effects
Chromones: PD, pharmacology
Culture Media, Serum-Free: PD, pharmacology
Dose-Response Relationship, Drug
***Endothelium, Vascular: CY, cytology**
Endothelium, Vascular: DE, drug effects
***Endothelium, Vascular: ME, metabolism**
Enzyme Inhibitors: PD, pharmacology
Humans
Morpholines: PD, pharmacology
Neoplasm Proteins: ME, metabolism

Neoplasm Proteins: PD, pharmacology
Phosphorylation
*Protein-Serine-Threonine Kinases
*Proteins:. . .
CN 0 (Androstadienes); 0 (Angiopoietin-2); 0 (Chromones); 0 (Culture Media, Serum-Free); 0 (Enzyme **Inhibitors**); 0 (MEN1 protein, human); 0 (Morpholines); 0 (Neoplasm Proteins); 0 (Proteins); 0 (Proto-Oncogene Proteins); EC 2.7.1.112 (Receptor, TIE-2); EC 2.7.1.137. . .

L10 ANSWER 9 OF 10 MEDLINE on STN
TI Tumor necrosis factor-alpha upregulates angiopoietin-2 in human umbilical vein **endothelial** cells.
AU Kim I; Kim J H; Ryu Y S; Liu M; Koh G Y
PY **2000**
SO Biochemical and biophysical research communications, **(2000 Mar 16)** 269 (2) 361-5.
Journal code: 0372516. ISSN: 0006-291X.
TI Tumor necrosis factor-alpha upregulates angiopoietin-2 in human umbilical vein **endothelial** cells.
SO Biochemical and biophysical research communications, **(2000 Mar 16)** 269 (2) 361-5.
Journal code: 0372516. ISSN: 0006-291X.
AB The angiopoietin-Tie2 system is an important regulator of vasculogenesis and vascular integrity. Angiopoietin-2 (**Ang2**) disrupts blood vessel formation in the developing embryo by antagonizing the effects of angiopoietin-1 (Ang1) on the Tie2 receptor. In this study, we examined the effect of a well-known proinflammatory cytokine, tumor necrosis factor-alpha (TNF-alpha), on **Ang2** expression in human umbilical vein **endothelial** cells. Reverse transcriptase-polymerase chain reaction and Northern blot analyses indicated that TNF-alpha induced **Ang2** mRNA expression in a time- and dose-dependent manner. Western blot analyses revealed that TNF-alpha treatment increased cellular **Ang2** protein. TNF-alpha induced less **Ang2** mRNA expression in the presence of nuclear factor-kappaB (NF-kappaB) **inhibitor**. These results suggest that TNF-alpha-induced inflammatory **angiogenesis** might be facilitated by the induction of **Ang2**.

CT Angiopoietin-2
Base Sequence
DNA Primers
Endothelium, Vascular: CY, cytology
***Endothelium, Vascular: DE, drug effects**
Endothelium, Vascular: ME, metabolism
Humans
NF-kappa B: AI, antagonists & inhibitors
Neovascularization, Pathologic: GE, genetics
*Proteins: GE, genetics
RNA, Messenger: GE, genetics
Recombinant Proteins: PD,. . .

L10 ANSWER 10 OF 10 MEDLINE on STN
TI Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis.
AU Maisonpierre P C; Suri C; Jones P F; Bartunkova S; Wiegand S J; Radziejewski C; Compton D; McClain J; Aldrich T H; Papadopoulos N; Daly T J; Davis S; Sato T N; Yancopoulos G D
PY **1997**
SO Science, **(1997 Jul 4)** 277 (5322) 55-60.
Journal code: 0404511. ISSN: 0036-8075.
SO Science, **(1997 Jul 4)** 277 (5322) 55-60.
Journal code: 0404511. ISSN: 0036-8075.
AB **Angiogenesis** is thought to depend on a precise balance of positive and negative regulation. Angiopoietin-1 (Ang1) is an angiogenic factor that signals through the **endothelial** cell-specific Tie2 receptor tyrosine kinase. Like vascular **endothelial** growth factor, Ang1 is essential for normal vascular development in the mouse. An Ang1 relative, termed angiopoietin-2 (**Ang2**), was identified

by homology screening and shown to be a naturally occurring antagonist for Angl and Tie2. Transgenic overexpression of **Ang2** disrupts blood vessel formation in the mouse embryo. In adult mice and humans, **Ang2** is expressed only at sites of vascular remodeling. Natural antagonists for vertebrate receptor tyrosine kinases are atypical; thus, the discovery. . .

CT . . .

Acid Sequence
Angiopoietin-1
Angiopoietin-2
Animals
Blood Vessels: EM, embryology
*Blood Vessels: ME, metabolism
Cells, Cultured
Cloning, Molecular
Embryo: ME, metabolism
Endothelial Growth Factors: GE, genetics
Endothelial Growth Factors: ME, metabolism
***Endothelium, Vascular: CY, cytology**
Endothelium, Vascular: ME, metabolism
Humans
Ligands
Lymphokines: GE, genetics
Lymphokines: ME, metabolism
Membrane Glycoproteins: AI, antagonists & inhibitors
Membrane Glycoproteins: ME, metabolism
Mice
Mice, Transgenic
Molecular Sequence Data
*Neovascularization, Physiologic
Phosphorylation
Proteins: CH, chemistry
*Proteins: ME, metabolism
Rats
Rats, Sprague-Dawley
***Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors**
Receptor Protein-Tyrosine Kinases: ME, metabolism
Receptor, TIE-2
Recombinant Fusion Proteins: ME, metabolism
Research Support, Non-U.S. Gov't
Signal Transduction
Vascular Endothelial Growth Factor A
Vascular Endothelial Growth Factors

CN 0 (Agpt protein, mouse); 0 (Agpt protein, rat); 0 (Angiopoietin-1); 0 (Angiopoietin-2); 0 (**Endothelial** Growth Factors); 0 (Ligands); 0 (Lymphokines); 0 (Membrane Glycoproteins); 0 (Proteins); 0 (Recombinant Fusion Proteins); 0 (Vascular **Endothelial** Growth Factor A); 0 (Vascular **Endothelial** Growth Factors); EC 2.7.1.112 (Receptor Protein-Tyrosine Kinases); EC 2.7.1.112 (Receptor, TIE-2)